Project 4: Drug development programs: S1R agonists, FENM and beyond (project leader: Tangui Maurice)

S1R is specifically enriched in MAMs, where it interacts with several proteins involved in ER-mitochondria Ca^{2+} transfer and/or activation of the ER stress pathways. By stabilizing the conformation of IP_3R at MAM, S1R increases Ca^{2+} efflux into mitochondria. S1R therefore represents a compelling target for the pharmacological treatment of several neurodegenerative diseases and a highly pertinent target to correct MAM dysfunction. Determining the impact of MAM alterations in neurodegenerative process and on S1R expression and/or activity is a promising track for the development of effective cytoprotective and putatively disease-modifying treatments. Through several long-lasting collaborations with medicinal chemists, we screen, analyze and validate in vitro and in vivo novel **innovative S1R agonists as neuroprotectants** in neurodegenerative diseases.

We are incubating a novel start-up company, ReST Therapeutics, that develop **Fluoroethylnormemantine** as an anxiolytic drug in post-traumatic stress disorders and as a neuroprotectant drug in AD. Demonstration of its effectiveness in non-transgenic and transgenic models of AD, in comparison of its parent drug Memantine, comprehension of its mechanism of action and optimization of its delivery route are on going as a collaboration between ReST Therapeutics and the group.

A last but very active line of research concerns the development of multi-acting, innovative hybrid molecules carrying a **butyrylcholinesterase inhibitory activity** that appreaed highly effrective as neuroprotectants in AD rodent models. The collaboration with the group of Michael Decker expands the landscape of promising innovative compounds with unique mode of action.

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